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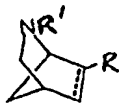

(I)

(II)

(57) Abstract

The present invention relates to novel epibatidine analogues which has formula (I) wherein R represents an alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or (hetero)arylalkyl group, said group optionally being substituted by one or more: alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, (hetero)arylalkyl, haloalkyl, amino, alkylamino amido or sulphonamido groups, R' represents hydrogen, alkyl or a nitrogen protecting group and (II) represents a single or double bond.

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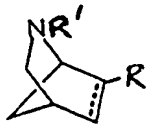
EPIBATIDINE ANALOGUES AS ACETYLCHOLINE RECEPTOR ANTAGONISTS

This invention relates to epibatidine analogues.

Epibatidine has attracted considerable attention from the scientific community due to its novel structure combined with the fact that it is a highly potent non-opiod analgesic nicotinic acetyl choline receptor (nAChR) agonist. Unfortunately epibatidine is toxic or even lethal at doses only slightly higher than its effective analgesic dose. Accordingly epibatidine appears not to have a future. On the other hand, it is a significant therapeutic lead in the important search for nAChR modulators having a wider separation between antinociceptive and toxic effects.

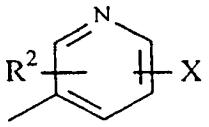
The present invention concerns related compounds in which the nitrogen bridge in epibatidine is modified by the introduction of a methylene group. According to the present invention there is provided a compound of the formula



wherein R represents an alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or (hetero)arylalkyl group, said group optionally being substituted by one or more: alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, (hetero)arylalkyl, haloalkyl, amino alkylamino, amido or sulphonamido groups, R^1 represents hydrogen, alkyl or a nitrogen protecting group, and ----- represents a single or double bond.

Typically, the alkyl, alkoxy, alkenyl and alkynyl groups contain 1 to 6, especially 1 to 4 carbon atoms, for

example butyl. The aryl groups are preferably phenyl while typical hetero aryl groups include thienyl, furyl, and nitrogen-containing groups, including those which do not contain oxygen such as pyridyl, imidazolyl, pyrazinyl and pyrimidyl, pyridyl being preferred. Thus R preferably represents the formula

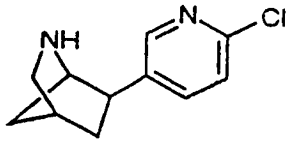


wherein X represents hydrogen, halogen eg. bromine, iodine, or chlorine which is especially preferred or haloalkyl and R^2 represents hydrogen or alkyl.

R' preferably represents hydrogen. Typical nitrogen protecting groups include tertiary butoxycarbonyl, which is preferred, methoxycarbonyl, phenylmethoxy and alkoxy.

Preferably the bicycloheptyl ring is fully saturated.

The preferred compound of the present invention is 6-(6-chloro-3-pyridinyl)-2-azabicyclo [2.2.1]-heptane, especially the endo enantiomer, which has the formula



Other specific compounds of the present invention include those where R is butyl or phenyl (and R' may be hydrogen). The compounds of this invention are isomers of epibatidine and its analogues in which the nitrogen in the rigid

bicycloheptane framework is translocated from the 7- to the 2- position but maintains the same connectivity and similar relative orientation to the chloropyridyl, for example, substituent. They are desirably in the endo form and preferably are in the form of a single optical isomer of the endo enantiomers or is predominantly, i.e. not a racemic mixture, a single enantiomer.

It is believed that these compounds will have utility particularly for the relief of pain, especially as analgesics, in pharmaceutical preparations. Studies have shown that the preferred compound (as a racemic mixture) is a potent nicotinic agonist and binding studies (competitive assay against [H3] epibatidine in rat brain P2 membranes) gives a Ki value of 0.26 nM compared to 0.036 nM for epibatidine. Accordingly, the present invention also provides a pharmaceutical compound which comprises a composition of the present invention and a pharmaceutically acceptable diluent or carrier.

The compounds of the present invention can be administered by any suitable route in a dose effective for the treatment intended. These doses can be readily ascertained by one of ordinary skill in the art. The compounds may, for example, be administered parentally, for example intravascularly, intraperitonially, subcutaneously or intramuscularly, or topically.

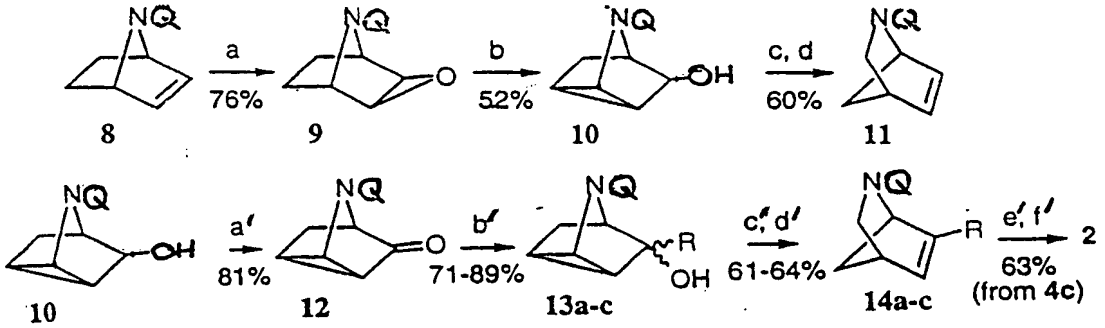
For oral administration, the compositions are typically in the form of a tablet, capsule, suspension or liquid, if desired in the form of a dosage unit such as a tablet or capsule.

If the compositions are for oral administration, typical diluents and carriers include lactose, sucrose, starch powder, cellulose esters of alkanoic acids,

cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulphuric acids, gelatine, acacia gum, sodium alginate, polyvinyl pyrrolidone and polyvinyl alcohol. Formulations for parental administration are typically in the form of aqueous or non-aqueous isotonic sterile injectable solutions or suspensions, for example saline or a dextrose solution.

Possible doses for the compounds of the present invention include from 0.1 to 20 micro grams per kilogram body weight per parental dose, especially from about 1 to 6 micro grams per kilogram body weight.

The compounds of the present invention can be prepared according to the reaction schemes shown below.



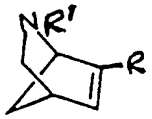
14 a:R=Bu; b:R=Ph; c:R=6-Cl-3-pyridinyl

Thus the starting material is the known alkene 8 which can be obtained in 3 steps from N-butyloxycarbonyl (Boc) pyrrole and tozylethyne, as described in Tetrahedron Letters, 1996, 37, 2201-2204. For simplicity, Q represents Boc in the reaction scheme although it will be appreciated that other nitrogen protecting groups of Q can be used. The

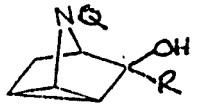
conversion of 8 to 9 (typically 76%; all the percentages represent actual, but typical values) involves epoxidation and base induced rearrangement of the epoxide 9 gives rise to azanortricyclanol 10 (52%). The epoxide 9 is achiral so that the rearrangement will normally give rise to a racemate. However the use of a chiral base will give rise to a stereospecific product i.e. either optical isomer of the endo enantiomer. Radical deoxygenation of 10 gives 11 as the only isolated product (60%).

To prepare the compounds in which R is not hydrogen, e.g. 14 a, b and c it is necessary to convert the alcohol 10 to the ketone 12 by oxidation (81%). The ketone can then be converted to the substituted alcohol, 13, usually as an epimeric mixture, using a reducing agent such as a lithium derivative corresponding to the substituent R (84%). Radical deoxygenation of 13 gives rise to 14 (61%).

One of the key steps of this process is the radical deoxygenation step. This is because radical deoxygenation could, in the case of a substituent R, give rise to three different products depending on the position of the free radical formed. Indeed with a carbocyclic ring, as opposed to a nitrogen-containing ring, one does normally obtain roughly equal amounts of the two possible isomers. It is a surprising feature that the process appears to follow almost exclusively a path resulting from the generation of a free radical at the OH carbon atom. This process does, therefore, constitute another aspect of the present invention. Accordingly, the present invention also provides a process for preparing a compound of the formula



wherein R & R' are as defined above which comprises subjecting a compound of the formula



wherein Q represents a protecting group, to radical deoxygenation.

It is preferred that the protecting group forms a carbamate or thiocarbamate group with the nitrogen atom or, alternatively, is a triphenylmethyl group. It is believed that the formation of the carbamate or thiocarbamate enables amide-type resonance to take place with the blocking group thus stabilising the radical (7) formed from the initial radical (6).

6 7

Alternatively, or additionally, the desired isomer is obtained due to a larger CH-N-CH angle in 7 (compared with 6) which promotes amide-type resonance. In particular, therefore, Q represents butyloxycarbonyl, preferably tertiary butyloxycarbonyl, methyloxycarbonyl or methylthiocarbonyl.

The radical deoxygenation can be carried out typically following the procedures of Barton *et al*, J Chem Soc Perkin Trans 1 1975, 1574-1575. This involves the use of, typically, potassium hydride followed by carbon disulphide and free radical generator such as methyliodide, and

tributyl tin hydride. It has been found that when R is not hydrogen the deoxygenation is best carried out using the procedure of Dollan & MacMillan (J Chem Soc Chem Commun 1985, 1588-1589) where the reactants are $ClCOCO_2Me$ with a base such as dimethylaminopyridine and methyl cyanide, and, as before tributyl tin hydride.

The specific reaction conditions which were used are set out below.

(a) Oxone (15eq.), $(EDTA)Na_2$ (0.05 eq.), acetone (15 eq.), Bu_4NHSO_4 (0.2 eq.), $NaHCO_3$ (30 eq.), 1:2 CH_2Cl_2/H_2O, 25°C, 48h; (b) LDA (1.6 eq.), Et_2O, 0°C, 5 min; (c) KH (1.5 eq.), THF, 0°C, 20 min, then CS_2 (1.3 eq.), 0°C, 10 min, then MeI (1.3 eq.), 20 min; (d) Bu_3SnH (1.6 eq.), AIBN, toluene, 110°C, 1 h.

(a') $(CO)_2Cl_2$(2.4 eq.), DMSO (2.4 eq.), CH_2Cl_2, -78°C, 20 min then NEt_3 (6 eq.); (b') RLi (2.5 eq.), 1:1 THF/Et_2O, -78°C to 25°C, 2h; (c') $ClCOCO_2Me$ (1.3 eq.), DMAP (1.5 eq.), MeCN, 25°C, 30 min; (d') Bu_3SnH (1.5 eq.), AIBN, toluene, 100°C, 1 h; (e') H_2 (1 atm.), 10% Pd/C, EtOAc, 25°C, 20 min; (f') TFA (37 eq.), CH_2Cl_2, 25°C, 2 h.

If it is desired to retain the double bond in the compounds of formula 11 and 14 then it is necessary simply to de-protect the nitrogen atom in known manner. On the other hand, if the saturated compound is required then it is necessary first to hydrogenate, for example with palladium (77%), and then to de-protect (82%).

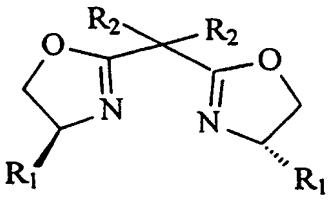
The ketones 12 are believed to be novel and therefore form another aspect of the present invention. In particular, 3-(tert-butoxycarbonyl)-3-azatricyclo[2.2.1.0.2,6]heptan-5-one possesses the following characteristics:

δH (200 MHz, $CDCl_3$, $CHCl_3$, *J* /Hz) 4.33 (1 H, d, *J* 4.5 C(4)H), 3.74 (1 H, s, C(2)H), 2.30-2.34 (1 H, m, C(6)H),

2.03 (1 H, D, *J* 10.0, H of CH_2), 1.76 (1H, dt, *J* 11.0, 2.0, H of CH_2), 1.60 (1 H, t, *J* 5.0, C(1) and 1.46 (9 H, s, But).

As indicated above, it is possible to obtain the specific enantiomer, 10, desired using a chiral base. In particular it has been found that the use of an aryl lithium compound in the presence of a chiral base such as (-)-sparteine or a bisoxazoline gives better yields than alkyl lithiums. Further the use of a more sterically hindered aryl lithium improved the enantiomer excess, *ee*. Thus the inclusion of a methyl group ortho to the Li ion, optionally with another C_1-C_4 alkyl group in the para position, is useful although 3 substituents on the phenyl ring is too hindered i.e. in general the phenyl ring should have 1 or 2 substituents, typically C_{1-4} alkyl such as methyl. Specific compounds which give good *ees* include 2-tolyl lithium and 2-methyl-4-anisyl lithium.

It has also been found that the combination of specific aryl lithium and specific bisoxazoline can be important both for yield and ees. The bisoxazolines typically have the formula:



where each R_1 and R_2, which may be the same or different, is an alkyl substituent, typically of 1 to 4 carbon atoms, such as ethyl, isopropyl, isobutyl and tert. butyl. Preferred compounds include valine and tert. leucine derived ligands where R_1 = isopropyl or tert.butyl and R_2 = ethyl or R_1 = isopropyl and R_2 = isobutyl. Too much steric hindrance in the combination tends to reduce yields.

The following Examples further illustrates the present invention.

Example 1

Preparation of the compound of formula 14 where R is 6-chloro-3-pyridenyl

DMAP (114 mg. 0.93 mmol) and $ClCOCO_2Me$ (0.09 cm^3, 0.98 mmol) were added to a stirred solution of alcohol 13c (200 mg, 0.62 mmol) in MeCN (12 cm^3) at 25°C. After 30 min the reaction mixture was diluted with EtOAc (20 cm^3) and washed with $NaHCO_3$ (10 cm^3) and H_2O (10 cm^3). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure to give the crude oxalyl ester as a yellow oil (252 mg) which then was co-evaporated twice with toluene. AIBN (*ca.* 20 mg) and Bu_3SnH (0.27 cm^3, 1.00 mmol) were added to a stirred solution of the crude oxalyl ester in dry, degassed toluene (15 cm^3) and the reaction mixture was then heated to 100°C. After 45 min the reaction mixture was allowed to cool and then evaporated under reduced pressure to give a yellow oil which as treated exactly according to the procedure of Curran and Chang (Curran, D.P.; Chang, C-T. *J.Org. Chem.* 1989, 54, 3140-3157) to remove the tin byproducts. Final purification by column chromatography [40% Et_2O-light petroleum (b.p. 40-60°C)] gave 14c as a colourless oil (115 mg, 61%): R_f0.61 [75% Et_2O-light petroleum (b.p. 40-60°C]; ν_{max}(neat)/cm^{-1} 2975m, 1691s, 1464m, 1408s, 1337s,

1157s and 1106s; δH(270 MHz; $CDCl_3$; *J*/Hz) 8.58 (1 H, br s, C(2 of pyridine)H), 8.00 and 7.78 (1 H, 2 x d, *J* 8.5, C(4 of pyridine)H), 7.30 (1 H, d, *J* 9.0, C(5 of pyridine)H), 6.62 and 6.54 (1 H, 2 x br s, C=CH), 5.04 (1 H, br s, C(1)H), 3.47 (1 H, dd, *J* 90 and 3.0, H of $C(3)H_2$), 3.34 (1 H, br s, C(4)H), 2.82 and 2.73 (1 H, 2 x d, *J* 9.5, H of $C(3)H_2$), 1.78 (2 H, d, *J* 7.5, $C(7)H_2$) and 1.43 (9 H, s, Bu^t); δC(100 MHz; $CDCl_3$) (2:1 mixture of rotational isomers observed) 155.0 (C=O), 150.0 (CH=*C*), 146.8 (C2 of pyridine), 143.7 (C6 of pyridine), 137.2 (C3 of pyridine), 136.0 and 135.3 (C4 of pyridine), 131.8 and 131.5 (*C*H=C), 124.0 and 123.9 (C5 of pyridine), 80.1 (CMe_3), 61.5 and 61.4 (C1), 48.2 and 47.9 (C7), 46.9 and 46.3 (C3), 44.2 and 43.5 (C4) and 28.5 (3 x Me); *m/z* (CI, NH_3) 307/309 ($M+H^+$, 90%), 267 (10), 251 (20) and 223/225 (100) (Found: $M+H^+$, 307.1224. $C_{16}H_{19}ClN_2O_2$ requires *M*, 307.1213). Removal of the protecting group gave

6-(6-chloro-3-pyridyl)-2-azabicyclo (2.2.1] heptane: δH (500 MHz, CD_3OD, CH_3OH, J/Hz) 8.31 (1 H, d, J 2.5, C(2 of pyridine)H), 7.78 (1 H, dd, J 10.5, 2.5, C(4 of pyridine)H), 7.45 (1 H, d, J 8.5, C(5 of pyridine)H, 3.63 (1 H, s, C(1)H), 3.44-3.41 (1 H, m, C(6)H), 2.95-2.92 (1 H, m, H of CH_2, 2.77 (1 H, d, J 9.5, H of CH_2), 2.60 (1H, s, C(4)H), 2.22-2.16 (1 H, m, H of CH_2), 1.90-1.79 (2 H, m, H of CH_2) and 1.67-1.63 (1 H, m, H5).

Example 2

The yields and ees for the conversion of the epoxide 9 where Q = Boc to the alcohol, 10 were investigated for different lithium compounds in the presence of (-)-sparteine. The results obtained are shown in Table 1. The reactions were carried out using 3 equivalents of each of

the Li compound and sparteine at -78°C in Et_2O for 5 hours and then warming to ambient temperature over 12 hours.

RLi	Yield	*Ee*
Bu^sLi	12%	65%
PhLi	50%	59%
PhLi	61%	49%
2-TolylLi	61%	77%
2-Methyl-4-anisylLi	60%	77%
MesitylLi	43%	15%

Example 3

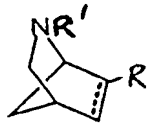
Example 2 was repeated using various bisoxazolines in place of sparteine. The results obtained are shown in Table 2.

Bisoxazoline	Base	Yield[a]	*Ee*
($R_1=Pr^i$, $R_2=Et$)	Bu^sLi	37% (51%)	63%
($R_1=Pr^i$, $R_2=Et$)	PhLi	36% (66%)	76%
($R_1=Pr^i$, $R_2=Et$)	2-TolylLi	53% (64%)	82%
($R_1=Pr^i$, $R_2=Et$)	2-Methyl-4-anisylLi	63%	83%
($R_1=Bu^t$, $R_2=Et$)	PhLi	15% (26%)	74%
($R_1=Bu^t$, $R_2=Et$)	2-Methyl-4-anisylLi	40% (60%)	72%
($R_1=Pr^i$, $R_2=Bu^i$)	PhLi	51%	87%
($R_1=Pr^i$, $R_2=Bu^i$)	2-Methyl-4-anisylLi	21% (75%)	65%

[a]yield in parentheses based on recovered epoxide 1.

CLAIMS

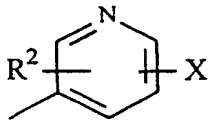
1. A compound of the formula



wherein R represents an alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or (hetero)arylalkyl group, said group optionally being substituted by one or more: alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, (hetero)arylalkyl, haloalkyl, amino, alkylamino amido or sulphonamido groups, R' represents hydrogen, alkyl or a nitrogen protecting group and ----- represents a single or double bond.

2. A compound according to claim 1 wherein R represents pyridyl.

3. A compound according to claim 2 wherein R represents the formula:



wherein X represents hydrogen, halogen or haloalkyl and R^2 represents hydrogen or alkyl.

4. A compound according to claim 3 wherein R^2

represents hydrogen and X represents chlorine.

5. A compound according to any one of the preceding claims wherein ----- represents a single bond.

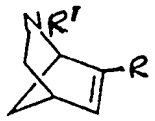
6. A compound according to any one of the preceding claims wherein R' represents hydrogen.

7. A compound according to any one of claims 1 to 5 wherein R' represents tertiary butoxycarbonyl.

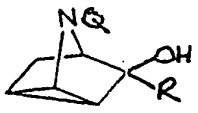
8. 6-(6-Chloro-3-pyridinyl)-2-azabicyclo [2.2.1] hept-5-ene.

9. A compound according to any one of the preceding claims which is in the form of a single enantiomer or is predominantly a single enantiomer.

10. A process for preparing a compound of the formula:



wherein R and R' are as defined in claim 1 which comprises subjecting a compound of the formula



wherein Q represents a protecting group, to radical deoxygenation.

11. A process according to claim 10 wherein Q represents a group which forms a carbamate or triocarbamate group with the nitrogen atom, or is a triphenylmethyl

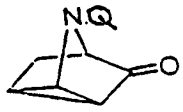
group.

12. A process according to claim 11 wherein Q represents butyloxycarbonyl, methyloxycarbonyl or methylthiocarbonyl.

13. A process according to any one of claims 10 to 12 wherein the radical deoxygenation is carried out by generating a free radical at the hydroxyl carbon atom with reaction with tributyl tin hydride.

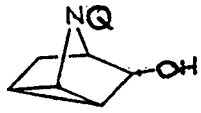
14. A process according to any one of claims 10 to 13 wherein the resulting compound is hydrogenated and/or de-protected.

15. A process according to any one of claims 10 to 14 wherein the starting material where R is not hydrogen is obtained by reacting the ketone of the formula:



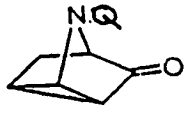
with RLi.

16. A process according to claim 15 wherein the ketone is obtained by oxidising the alcohol of the formula:



17. A process according to claim 10 substantially as hereinbefore described.

18. A ketone of the formula:



wherein Q is as defined in any one of claims 10 to 12.

19. The ketone according to claim 18 wherein Q represents butoxycarbonyl.

20. A pharmaceutical composition which comprises a compound as claimed in any one of claims 1 to 9 or obtained by a process as claimed in any one of claims 10 to 17 and a pharmaceutically acceptable diluent or carrier.

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/GB 99/03175

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/52 C07D401/04 A61K31/4427

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FLOERSHEIM, PHILIPP ET AL: "Isosterism and bioisosterism case studies with muscarinic agonists" CHIMIA (1992), 46(7-8), 323-34 , XP002125102 compounds 37,38 ---	1,20
X	WO 95 10513 A (PFIZER ;CAMERON KIMBERLY O (US); SILVA JARDINE PAUL DA (US); LARSO) 20 April 1995 (1995-04-20) page 75, line 5 ---	1
X	EP 0 582 829 A (AMERICAN CYANAMID CO) 16 February 1994 (1994-02-16) example 35 --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 December 1999	04/02/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	De Jong, B

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INTERNATIONAL SEARCH REPORT

Inter onal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	POMBO-VILLAR ET AL: "6-carboxymethyl-2-azabicyclo‘2.2.2!-heptane enantiomers" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 2, no. 5, 1992, pages 501-504, XP000863366	1,20
A	WO 92 05172 A (PFIZER LTD ;PFIZER (US)) 2 April 1992 (1992-04-02) examples	1
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P,X	HODGSON, DAVID M. ET AL: "An epoxide rearrangement. Radical rearrangement approach to 6-substituted 2-azabicyclo‘2.2.1!-5-heptenes. Synthesis of an epibatidine analog" SYNLETT (1998), (12), 1349-1350 , XP002125103 the whole document	1-20
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INTERNATIONAL SEARCH REPORT

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